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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,138	11/06/2006	David Wallach	30694/41889	3144
4743 7590 12/03/2009 MARSHALL, GERSTEIN & BORUN LLP 233 SOUTH WACKER DRIVE 6300 SEARS TOWER CHICAGO, IL 60606-6357				
EXAMINER				
WEN, SHARON X				
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1644				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/573,138

Applicant(s)

WALLACH ET AL.

Examiner

SHARON WEN

Art Unit

1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 September 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17, 19-56 and 65-83 is/are pending in the application.
- 4a) Of the above claim(s) 17, 39-56 and 65-83 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-16 and 19-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Applicant's amendment, filed 09/01/2009, has been entered.

Claims 18, 57-64 and 84-85 have been canceled.

Claims 1-17, 19-56 and 65-83 are pending.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 04/30/2009 is acknowledged. The traversal is on the ground(s) that Rothe et al. (U.S. Patent 5,854,003) does not destroy the special technical feature of the instant claims because Rothe et al. taught a mutant NIK polypeptide containing a substitution at position 25 compared to the NIK sequence of the instant application. This is not found persuasive for the following reasons:

Given the recitation of "an amino acid sequence, or a portion of said amino acid sequence" in the independent claims, the instant claims are broadly drawn to an antibody that binds any portion of the amino acid sequences selected from the recited peptides of NIK. Rothe et al. taught immunizing rabbit with the NIK polypeptide. Even though Rothe's NIK polypeptide contains a substitution at position 25, one of ordinary skill in the art would have recognized that the polyclonal antiserum generated by immunizing rabbits with Rothe's NIK would necessarily bind to at least a portion of the amino acid sequence contained in any one of the peptides recited in the instant claims because polyclonal antibodies are known to bind multiple epitopes.

The requirement is still deemed proper and is therefore made FINAL.

Upon further consideration, the examination has been extended to SEQ ID NO: 11 and 12.

Claims 17, 39-56 and 65-83 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention/species, there being no allowable generic or linking claim.

Claims 1-16 and 19-38 are currently under examination as they read on a composition or a preparation comprising an antibody that binds a peptide of NIK set forth in SEQ ID NO: 7, 11 or 12, the hybridoma producing the antibody.

Claim Objections

Claims 1-2 are objected to because of the following informalities:

Given the recitation of "selected from...or" and "selected from...and/or", claims 1 and 2 are construed as Markush claims. Therefore, Applicant's is invited to amend the claims to recite the proper Markush language, i.e., "selected from the group consisting of...and".

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the limitation "*the* flank region of the NIK kinase domain". However, there is insufficient antecedent basis for this limitation in the base claim 1. Furthermore, one of ordinary skill in the art would not be reasonable apprised of which flanking region, i.e., 5' or 3' of the kinase domain, the claim is directed to. Therefore, the metes and bounds of the claim is indefinite. Applicant is invited to amend the claim to recite "a flank region of a NIK kinase domain" in order to obviate this rejection.

Claim 36 is drawn to a pharmaceutical composition comprising the antibody or the antibody fragment of claim 30 that is derived from a mouse. However, claim 30 recites that the antibody is a human antibody. Therefore, claim 36 is indefinite as to whether the antibody or the antibody fragment is mouse or human.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antibody fragment selected from the group consisting of a single chain Fv, an Fab, and Fab' and an F(ab')₂, does not reasonably provide enablement for **a CDR**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The breadth of the instant claims encompass an antigen-binding antibody fragment in which **fewer than all of the six CDRs** found in the heavy plus light chain pair that forms the binding region of a referenced antibody are defined. Therefore, the following grounds of rejection have been set forth.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding

myeloma protein resulted in the loss of antigen-binding function. MacCallum et al. J. Mol. Biol. (1996) 262, 732-745, analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.). Pascalis et al. (The Journal of Immunology (2002) 169, 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, *some residues in all 6 CDRs were used for the constructs* (see page 3080, left col.). The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset et al. (BBRC 2003, 307:198-205), which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, *clearly other CDRs play an important role in the recognition process* (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left col.). Vajdos et al. (J. Mol. Biol. (2002) 320, 415-428), additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.). Chen et al. (J. Mol. Bio. (1999) 293, 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu et al. (J. Mol. Biol. (1999) 294, 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany

antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation. Padlan et al. (PNAS 1989, 86:5938-5942) described the crystal structure of an antibody-lysozyme complex where all 6 CDRs contribute at least one residue to binding and one residue in the framework is also in contact with antigen. Lastly, Lamminmaki et al. (JBC 2001, 276:36687-36694) describe the crystal structure of an anti-estradiol antibody in complex with estradiol where, although CDR3 of VH plays a prominent roll, all CDRs in the light chain make direct contact with antigen (even CDR2 of VL, which is rarely directly involved in hapten binding).

Thus the state of the art recognized that it would be highly unpredictable that an antibody or the antigen-binding fragment thereof comprising less than all six CDRs from both the VH and VL regions with a desired specificity would bind the same antigen. Thus the minimal structure which provides the function of NIK-binding appears to include six CDRs (three in the heavy chain variable region and three in the light chain variable region) from the same antibody.

The instant disclosure enabled the antibodies with both heavy and light chain variable regions for binding NIK peptides. For example, antibody NIK81 disclosed in the instant specification comprises both heavy and light chain variable regions as set forth and the respective 6 CDRs. The specification as filed did not provide any evidence showing that NIK81 with fewer than all 6 CDRs can bind NIK.

Without sufficient guidance, and in view of the unpredictability of the art, it would require undue experimentation of the skilled artisan to make or use the claimed antibodies or antigen-binding fragments thereof with less than all six CDRs in order to bind NIK and detect NIK by Western or ELISA as commensurate in scope with the instant specification.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claims 1-16 and 19-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody that binds the amino acid sequence set forth in SEQ ID NO: 7, 11 or 12, does not reasonably provide enablement for an antibody that binds **any** amino acid sequence or **any** portion of the amino acid sequences set forth in SEQ ID NO: 7, 11 or 12 for detecting NIK **or a mutein, functional derivative, active fraction, circularly permuted derivative, salt or a portion thereof**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Under the broadest reasonable interpretation, the present claims are broadly drawn to antibodies that bind to an amino acid sequence or a portion of the amino acid sequence which reads on variants or fragments of the peptides with any minimal consecutive 2 amino acids. However, other than the antibodies binding to the amino acid sequence set forth in SEQ ID NOs: 7, 11 or 12, there does not appear to be an actual reduction to practice of an antibody that binds other species of the genus encompassing the variants of SEQ ID NOs: 7, 11 or 12; nor is there a complete or partial structure of an antibody capable of binding all the species of the above mentioned genus in detailed drawing or through a structural chemical formula, e.g., sequence of the antibody.

Furthermore, a skilled artisan is well aware that such antibodies binding the amino acid sequences of SEQ ID NOs: 7, 11 or 12 would not reasonably be expected to be reactive with all members of the genus encompassing all the variants of the peptides. For example, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991; see entire document) disclosed that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody. Further, Li et al. (PNAS 77: 3211-3214, 1980; see entire document) disclosed that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Moreover, for instance, Houghten et al. (New Approaches to Immunization, Vaccines 86, Cold Spring

Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al. state (see page 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool."

Give that the instant specification disclosed that the claimed antibody is used for detection of NIK or a mutein, functional derivative, active fraction, circularly permuted derivative, salt or a portion thereof. One of skill in the art would not be able to use the antibody that binds to SEQ ID NO: 7, 11 or 12 to measure all the variants of SEQ ID NO: 7, 11 or 12 or detect NIK or a mutein, functional derivative, active fraction, circularly permuted derivative, salt or a portion thereof, because, as the state of the art discussed above, the antibody that binds SEQ ID NO: 7, 11 or 12 would not be able to bind to all the variants of the peptides or NIK.

Therefore, the specification, as-filed, provided insufficient guidance to lead a person of skill in the art to use the claimed antibodies that binds SEQ ID NO: 7, 11 or 12 to measure all the variants of SEQ ID NO: 7, 11 or 12 commensurate in scope of the instant disclosure.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant is invited to amend the claims to recite "the amino acid sequence of SEQ ID NO: 7, 11 or 12" and avoid the recitation of "a mutein, functional derivative, active fraction, circularly permuted derivative, salt or a portion thereof" in order to obviate this rejection.

Claims 24-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a biological deposit rejection.*

It appears that Pep 7-81.1, Pep 11-355.8 and Pep 12-629-62-18 hybridoma clones are required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the cell line. See 37 CFR 1.801-1.809.

It appears that the above mentioned hybridoma clones have been deposited with CNCM under the Budapest Treaty. However, in addition to the conditions under the Budapest Treaty, Applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Applicant's assurance will obviate this rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-16 and 30-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Schreiber et al. (US 6,822,138 B1, see entire document).

Schreiber taught a polyclonal antibody that binds specifically to NIK (see e.g., column 15, paragraph 4) and a pharmaceutical composition comprising the antibody as a modulator of NIK and a pharmaceutically acceptable carrier (see column 18, lines 41-49 and column 27, lines 32-43).

Although Schreiber et al. did not teach the polyclonal antibody to NIK to bind specifically to the peptides set forth in SEQ ID NO: 7, 11 or 12, given that polyclonal antibodies are known to bind multiple epitopes on one antigen, the prior art polyclonal antibody raised against NIK would necessarily bind to the epitopes comprising the amino acid sequences of SEQ ID NO: 7, 11 and 12.

Since the Office does not have a laboratory to test the prior art polyclonal antibody, it is Applicant's burden to provide objective evidence showing that Schreiber's polyclonal antibody raised against NIK does not bind to SEQ ID NO: 7, 11 or 12.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHARON WEN whose telephone number is (571)270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571)272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sharon Wen/
Examiner, Art Unit 1644
November 30, 2009